JUV-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#33/K.T. 4/15
RESPONSE

Examiner	:	Richard Schnizer
Group	:	1635
Applicants	:	Grigori N. Enikolopov et al.
Application No.	:	09/444,335
Confirmation No.	:	8515
Filed	:	November 19, 1999
For	:	TRANSGENIC MICE EXPRESSING FLUORESCENT PROTEIN IN MULTIPOTENT STEM AND PROGENITOR CELLS

New York, New York
April 7, 2003

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Hon. Commissioner for Patents
P.O. Box 2327
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RESPONSE TO FINAL OFFICE ACTION

This responds to the October 7, 2002 Final Office Action ("Office Action") in the above application. Applicants submit herewith a petition for three-month extension of time. With the extension, a response must be filed by April 7, 2003. Thus, this response is timely filed.

Claims 1–24 and 51–79 are pending. All of these claims stand rejected as being unpatentable under 35 U.S.C. § 103(a). Applicants traverse these rejections.

Part I

Claims 1–24, 51–71, 78, and 79 stand rejected as being obvious over Zimmerman[1] in view of Chiochetti[2] for reasons set forth in the 6/20/01 Final Office Action and the 10/4/00 Office Action. The Examiner contends that Zimmerman teaches a method of detecting neuronal stem cells in a transgenic animal comprising a lacZ transgene under the control of the promoter and second intron of the rat nestin gene. The Examiner acknowledges that Zimmerman does not teach measuring multipotent stem and progenitor cells in a live animal. Office Action, p. 3. The Examiner further contends that Chiochetti teaches that GFP is a more powerful tool than β-galactosidase to study gene expression and that GFP allows direct imaging of living cells and living tissues. On this basis, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify the method of Zimmerman by replacing β-galactosidase with Chiochetti's GFP for studying gene expression in neuronal stem cells in living animals and their organs and tissues.

Applicants traverse. Zimmerman and Chiochetti do not, alone or in combination, teach or suggest **whole body** imaging in a live mammal transgenic for a gene encoding a fluorescent protein. The Declaration of Dr. Hoffman describes that intense fluorescence in the brain was detectable externally, through the skull and the opaque skin of the claimed animal (Point 8, second paragraph). The transgenic animal could be examined alive and intact, without any surgery. Such external imaging provides invaluable real-time data for examining neurogenesis. **Whole body, external** imaging of a living mammal's internal organ using GFP was not achieved in the art until applicants' invention.

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[1] Zimmerman et al., *Neuron* 12:11–24, 1994.

[2] Chiochetti et al., *Biochim. Biophys. Acta* 1352:193–202, 1997.

Indeed, the Examiner himself admits that Zimmerman does not teach imaging in a "live animal" (*supra*). Chiochetti does not remedy this deficiency. Chiochetti at most suggests imaging "living cells" and "living tissues," which, before applicants' invention, required dissection if internal organs were to be examined.

In a rejection addressed below, the Examiner also cites Yeh[3] for teaching that "GFP can be monitored in intact, living embryos . . . ." (Office Action, p. 4). But this reference is inapposite. Yeh describes using GFP in *Drosophila* embryos and larvae, which are barely visible by the naked eye. Whole body imaging of *Drosophila* embryos is thus a far cry from whole body imaging of a mammal. A mammal is not only much larger but also covered by opaque skin.

In sum, the claimed invention allows whole body, external imaging of neural stem cells of a mammal transgenic for a fluorescent protein-encoding gene. Zimmerman in combination with Chiochetti fails to teach this.

Part II

Claims 51–79 stand rejected as being obvious over Zimmerman, Chiochetti, Yeh, Lois,[4] and Reynolds.[5] The Examiner applies the former three articles as discussed above. The Examiner further contends that Lois teaches studying migration of nueronal precursors in adult mammalian brain, and that Reynolds teaches that neuronal stem cells express nestin. On this basis, the Examiner concludes that a person of ordinary skill in the art would have been motivated to use a transgenic animal comprising a GFP sequence

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[3] Yeh et al., *Proc. Natl. Acad. Sci. USA* 92:7036-7040, 1995.

[4] Lois et al., *Science* 264:1145–1148, 1994.

[5] Reynolds et al., *Science* 255:1707–1710, 1992.

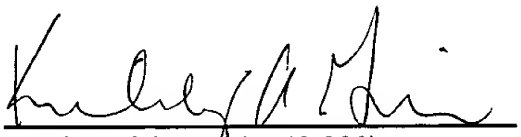
controlled by nestin regulatory sequences to follow neuronal precursor migration in living animals.

Applicants disagree. As discussed above, Zimmerman, Chiochetti, and Yeh together do not render obvious the use of the claimed transgenic animal for studying neural stem cells in a **live animal**. Neither Lois nor Reynolds talks about GFP transgenic animals and thus remedies this deficiency. Therefore, all five references as a whole do not render obvious the animals and methods of claims 51–79.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. Applicants invite the Examiner to telephone the undersigned if a telephonic discussion would facilitate resolution of outstanding issues in the case.

Respectfully submitted,



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